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Commentary OMICS International

Bringing Synthetic Optogenetics to the Clinic

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Commentary

The history and progress in neuroscience goes hand-in-hand with the development of tools, mostly because the brain is extremely difficult to study. Not only is it physically inaccessible, it also houses billions of different cells [1], interweaved in complex patterns of connectivity [2]. The advent of modern optical tools marks a new era for neuroscience; with optogenetics representing an emerging class of such transformative tools [3]. This method makes use of light (i.e., opto) to control the function of select proteins (i.e., genetics); to then modulate cellular function. Optogenetic tools make clever use of various light-sensitive proteins found in nature, known as photoreceptors. The outcome of photoreceptor activation on cellular function depends on the type of photoreceptor used. For example, increase in neuronal excitability can be obtained when a light-gated channel, specifically channelrhodopsin, is photoactivated [4,5]. Here, we would like to focus on a sister approach, recently titled synthetic optogenetics [6]. Synthetic optogenetics, which first emerged in 1968 [7], provides the means to control protein and cellular function by light, but with the help of synthetic chromophores; entitled photoswitches.

Photoswitches are synthetic molecules, typically composed from a blend of several chemical groups. All photoswitches bear a light-sensitive core (Figure 1a). Following light-absorption, the core undergoes changes, whether in geometry, length, or charge, and these are leveraged to propel changes in protein function. The other chemical groups of the photoswitch can consist of 'virtually' any other chemical moiety; for instance an inhibitor, ligand or even just a bulky or sticky chemical structure. These will typically determine the effect of the photoswitch on the protein it interacts with. In essence, a photoswitch incorporating an inhibitor will enable light-dependent inhibition of activity. The other added chemical groups can endow the photoswitch with additional properties to increase its' solubility, membrane permeability, photostability or to simply dock the photoswitch onto a particular side chain of a native or modified protein. Thus, in principle, synthetic optogenetics can engender any protein indirectly light-responsive.

The versatility of the method enables it to be used in a large variety of basic experimental paradigms. The method can be employed to study the role(s) of particular proteins in a cell, to drive action potential firing in neurons or used to understand the gating mechanism of ion channels, to name but a few examples. This versatility can also be extended towards the clinic. In fact, several groups have made significant strides in that direction, showing the ability of the approach to tackle chronic pain, vision impairments or cancer [8,9], but also see [6]. These reports show the potential of synthetic optogenetics in providing unique treatments—phototreatments— for diseases that are poorly addressed by current methods. Photo treatments may provide several key benefits over other methods (Figure 1).

Specificity

Photoswitches can be tethered to select proteins by various chemical means. This localizes and concentrates the 'photodrug' adjascent to its target, ensuring a more specific effect. Tethering allows selectivity even if the pharmacophore, used in the design of the photodrug, cannot distinguish between different proteins from the same family [10].

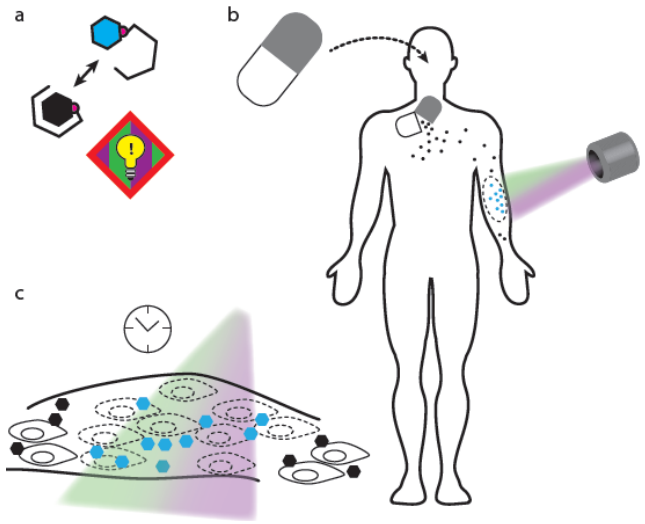

Figure 1: Phototreatment. a, Cartoon depiction of an inactive (black hexagon), light-sensitive (denoted by hazardous pictogram, below) photoswitch, or 'photodrug'. Light absorption by the photosensitive core (red circle) renders the photodrug active (cyan hexagone), and this process is reversible. b, Packaged photodrug (pill) is administered to a patient. The photodrug distributes across the patient's body and remains inactive, unless activated in a desired region (dashed circle on left arm) by light. c, The timing and duration (clock) of the photodrug's activity can be reversibly and temporally controlled by different wavelengths (magenta-green light beam). Photoactivation of the drug and activation of select proteins atop diseased cells causes cell death (dashed cells) in the desired region.

Side-effects

Activation of the photodrug by light can be performed in restricted regions of the patient (Figure 1b). This may reduce unwarranted

activity of the photodrug elsewhere in the body, thereby reducing unexpected or negative effects.

Resistance

The active drug could be activated and deactivated at will with different colors of light. This can be applied to limit the duration of the drug's activity at the intended region so as to lower the risk of the target tissue from developing resistance due to prolonged activity of the drug (Figure 1c).

However, we are still somewhat distant from reaching this goal, as discussed more in depth by Berlin et al. [6]. Despite the great efforts of multiple academic research groups, which are persistently pushing the technique forward, rapid development and optimization of the technique could greatly benefit from commercial entities, such as pharmaceutical companies. This type of alliance could present new opportunities for developing new phototreatment methodologies and technologies, which, in our opinion, 'outshine' the risks of this endeavour. Together, the synthetic optogenetic approach is yet an untapped resource and holds several unique advantages that are just waiting to be explored in the clinic. Who will be the first to take the leap to take the lead?

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